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Imaging Effects of Neurotrophic Factor Genes on Brain Plasticity and Repair in Multiple Sclerosis

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13. SUPPLEMENTARY NOTES

14. ABSTRACT The objective of this study is to develop a better biomarker for multiple sclerosis (MS) by combining genotype and imaging data. In this study, patients with MS undergo neurological evaluation to confirm diagnosis and determine disability level. They have blood drawn for genotyping, and undergo magnetic resonance imaging sensitive to both focal and diffuse effects in gray and white matter, including cortical thickness and subcortical volume measures, lesion volumetry, and voxel-based morphometry and diffusion imaging. We are continuing to progress with screening, enrollment, and testing of participants. We have encountered no adverse events. We continued to use our established procedures for acquiring, logging and backing up all data, and completing ongoing QA of the data. The genotyping will occur in batches; the blood samples are securely stored in our Molecular Diagnostics Laboratory until then. We are having biweekly to weekly research meetings, and additional meetings as needed, and I am monitoring the financial and administrative issues together with our Grants Manager. We are preparing a two conference submissions based on early results from this study, one on neurotrophic factor genotype as a predictor of hippocampal atrophy on MRI in MS, and one on a semi-automated program we have developed for MS lesion segmentation on fluid-attenuated inversion recovery images. These will be submitted to the International Neuropsychological Society for presentation at their Annual Meeting in Feburary 2011.

15. SUBJECT TERMS
Multiple sclerosis, MRI, genotype

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Table of Contents

Introduction

Background.   Conventional MRI p rovides a u seful b iomarker fo r multiple sclero sis (MS) cli nical trials, b ut conventional imaging is in sensitive to many of the neural changes in the disease and a better biomarker is n eeded. The propo sed study will combine multimodal MRI, to capture the full range of neural changes in the disease, with genotype data to develop a more sensitive and comprehensive biomarker for the disease. Neurotrophic factor genes related to brain plasticity and repair will be targeted for this purpose because of their probable moderating effects on neural damage in MS. Objective. The objective of the proposed study is to develop a better biomarker for MS by combining ge notype and imaging dat a.   Specific Ai ms.   We will co mbine d ata reg arding neurotrophic fact or genotype and imaging to: (1) Assess s pecific *a priori* hypotheses regarding effects of specific neurotrophic factor polymorphisms on specific brain imaging, (2) Assess both additive and interactive models of effects of genes within each of the three neurotrophic factor gene families on imaging of gray and white matter integrity, and (3) Determine the optimal linear combination of genotype and imaging data to predict concurrent level of disability in MS. Stu dy Design.   Patients with MS (N=200) will u ndergo neurological ev aluation to confirm d iagnosis an d determine disability level. Th ey will h ave blood drawn for genotyping, and will un dergo MR imag ing sensitive to both focal and diffuse effects in gray and white matter, in cluding cortical th ickness and subcortical v olume measures, lesion volumetry, and voxel-based morphometry and diffusion imaging. Regressio n and symbolic modeling will be used to ad dress th e specific ai ms. A n umber of d ata redu ction an d other procedures will be u sed to minimize Type II error. Im pact. This research will set th e stag e fo r future lo ngitudinal research assessin g th e obtained im aging-genotype biomarker as a predictor of d isease course and treatment response. Ultimately this research will improve the clinical care of patients with MS by increasing prognostic accuracy and enhancing our ability to identify optimal treatment prot ocols for individual patients. De velopment of a m ore sensitive a nd c omprehensive biomarker will contribute to drug discovery and clinical trials in MS.

Body
We are continuing to progress with screening, enrollment, and testing. We have encountered no adverse events. We continued to use our established procedures for acquiring, logging and backing up all data, and completing ongoing QA of the data. The genotyping will occur in batches; the blood samples are securely stored in our Molecular Diagnostics Laboratory until then. We are having biweekly to weekly research meetings, and additional meetings as needed, and I am monitoring the financial and administrative issues together with our Grants Manager. We are preparing a two conference submissions based on early results from this study, one on neurotrophic factor genotype as a predictor of hippocampal atrophy in MS, and one on a semi-automated program we have developed for MS lesion segmentation on fluid-attenuated inversion recovery images. Once the final results on these two projects are available they will be submitted to the International Neuropsychological Society for presentation at the Annual Meeting in Feburary 2011.

Key Research Accomplishments

- Abstract in preparation on neurotrophin genotype predictors of hippocampal atrophy, as measured using high-resolution imaging in MS
- Abstract in preparation on a semi-automated program we have developed for MS lesion segmentation on fluid-attenuated inversion recovery images

Reportable Outcomes

- two conference abstracts in preparation (noted above)
- grant application funded by the National MS Society to obtain standardized neuropsychological testing on participants in this study, to examine cognitive genetics in MS
- grant application submitted to request funding of a longitudinal extension of this study

Conclusion
The research protocol is approved and running as planned, with no adverse events encountered. Two conference submissions based on early results from this study are in preparation, we have obtained grant funding to add cognitive testing to the protocol for the purpose of studying neurotrophin gene effects on cognition in MS. We have also applied for funding of a longitudinal extension of the study, to follow participants over time to determine whether and which neurotrophin genes predict greater or lesser brain plasticity/ repair as measured using

quantitative brain imaging. The results of this study will improve scientific understanding of the factors that lead some patients with MS to progress at a more rapid rate, and others to have a more benign disease course, and will ultimately contribute to improved prognostication and treatment planning in the clinic.

References

Neurotrophin genotype and brain MRI of hippocampal atrophy in multiple sclerosis (in preparation)

Development and testing of a new approach to MS lesion segmentation using 3T FLAIR images (in preparation)

Appendices NA

Supporting Data NA